

WHO SPECIFICATIONS AND EVALUATIONS
FOR PUBLIC HEALTH PESTICIDES

TRANSFLUTHRIN

2,3,5,6-tetrafluorobenzyl (1*R*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate



**World Health
Organization**

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Disclaimer¹

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Compliance with the specifications does not constitute an endorsement or warranty of the fitness of a particular pesticide for a particular purpose, including its suitability for the control of any given pest, or its suitability for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular purpose and the content of the labelling instructions must be decided at the national or provincial level.

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¹ This disclaimer applies to all specifications published by WHO.

INTRODUCTION

WHO establishes and publishes specifications* for technical material and related formulations of public health pesticides with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

From 2002, the development of WHO specifications follows the **New Procedure**, described in the 1st edition of Manual for Development and Use of FAO and WHO Specifications for Pesticides (2002). This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by WHO and the experts of the “FAO/WHO Joint Meeting on Pesticide Specifications” (JMPS).

WHO Specifications now only apply to products for which the technical materials have been evaluated. Consequently, from the year 2002 onwards the publication of WHO specifications under the **New Procedure** has changed. Every specification consists now of two parts, namely the specifications and the evaluation report(s):

Part One: The Specification of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the 1st edition of the “FAO/WHO Manual on Pesticide Specifications.”

Part Two: The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by WHO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the “FAO/WHO Manual on Pesticide Specifications” and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

WHO specifications under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. WHO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

Specifications bear the date (month and year) of publication of the current version. Dates of publication of the earlier versions, if any, are identified in a footnote. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

* Footnote: The publications are available on the Internet under (<http://www.who.int/whopes/quality/en/>).

PART ONE

SPECIFICATIONS

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WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

TRANSFLUTHRIN

INFORMATION

ISO common name

transfluthrin

Synonyms

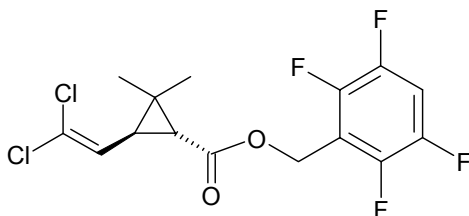
benfluthrin

Chemical names

IUPAC: 2,3,5,6-tetrafluorobenzyl (1*R*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

CA: (1*R*-trans)-(2,3,5,6-tetrafluorophenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate

Structural formula



Empirical formula

C₁₅H₁₂Cl₂F₄O₂

Relative molecular mass

371.16

CAS Registry number

118712-89-3

CIPAC number

741

Identity tests

GC retention time and IR spectrum (CIPAC Handbook K, p. 121, 2003); Enantioselective GC (CIPAC Handbook L, p. 128, 2006).

WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

TRANSFLUTHRIN TECHNICAL MATERIAL

WHO specification 741/TC (November 2006^{*})

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in evaluation reports (741/2002 and 741/2006). It should be applicable to TC produced by this manufacturer but it is not an endorsement of it, nor a guarantee that it complies with the specification. The specification may not be appropriate for TC produced by other manufacturers. The evaluation reports 741/2002 and 741/2006, as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of transfluthrin, together with related manufacturing impurities, and shall be a white to cream coloured crystalline powder, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (741/TC/(M)/2, CIPAC Handbook K, p.121, 2003; CIPAC Handbook L, p.128, 2005)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Transfluthrin content** (741/TC/(M)/3, CIPAC Handbook K, p.121, 2003)

The transfluthrin content shall be declared (not less than 965 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: <http://www.who.int/whopes/quality/en/>.

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EVALUATION REPORTS

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2002 Evaluation report based on submission of data from Bayer AG (TC)	11

WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

TRANSFLUTHRIN

EVALUATION REPORT 741/2006

Recommendation

The Meeting recommended that the specification for transfluthrin, proposed by Bayer CropScience*, should be adopted by WHO.

Appraisal

Data in support of a specification for transfluthrin TC were evaluated by the JMPS in 2002 (evaluation report 741/2002) but, at the request of the manufacturer, the specification was not published. In 2004, following submissions of additional information, the manufacturer stated that new 5-batch analytical data would be generated to support production of the TC at a new site and requested reconsideration of the data and proposed specification by the JMPS. The new data and a revised proposed specification for transfluthrin TC were submitted in 2005-6.

The Meeting was provided with commercially confidential information on:

- (i) the comparability of data with those submitted for registration in Australia;
- (ii) the manufacturing process at the new site;
- (iii) the names, structures and methods of analysis of impurities;
- (iv) data from analysis of 5 batches and the manufacturing specification at the new site.

The Australian Pesticides and Veterinary Medicines Authority (APVMA) confirmed that:

- (i) the new site manufacturing process described is essentially identical to that described in the data submitted for registration in Australia;
- (ii) the new site manufacturing specification for transfluthrin TC is identical to the declaration of composition provided for registration in Australia;
- (iii) the new site 5 batch analysis data provided to WHO comply with the declaration of composition provided for registration in Australia.

Material accountability in the 5-batch data from the new site was high (99.4-100.1%). One impurity had a reported limit of quantification (0.08 g/kg) above the stated manufacturing QC limit (0.02 g/kg). The impurity was non-relevant and the manufacturing specification for it was below the 1 g/kg threshold, therefore it was disregarded in considering whether or not the new manufacturing specification was within the earlier one. Nonetheless, the manufacturer explained that the impurity is monitored indirectly by determining the level of its precursor and, if the precursor is <0.02 g/kg, then the impurity is taken to be within the same limit.

* The manufacturer informed WHO that, in 2002, all Bayer AG assets related to crop protection and environmental science business, including the supporting data, were transferred to Bayer CropScience, which currently has the ownership.

The manufacturing process at the new site was identical to that at the previous site and the 5-batch data and manufacturing specification from the new site were all within the previous manufacturing specification. Thus a formal determination of equivalence by the Meeting was unnecessary.

WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

TRANSFLUTHRIN

EVALUATION REPORT 741/2002¹

Explanation

The data for transfluthrin were evaluated in support of a new WHO specification.

Transfluthrin is/was under patent in Barbados until 2002; Poland, Czech Republic, Slovakia, South Korea, Libya, Syria, Lebanon, Kuwait, Sri Lanka, China, Dominican Republic and Brazil until 2003; Jordan, Pakistan and Taiwan until 2004; Colombia until 2005; Panama until 2007; Denmark, Norway, Finland, Hungary, Pakistan, Malaysia, South Africa, Nigeria, Turkey, Israel, Ireland, Thailand, South Korea, Japan, USA, Mexico, El Salvador, Argentina, Australia and New Zealand until 2008; Canada until 2010.

Transfluthrin has not been evaluated by the FAO/WHO JMPR and WHO/IPCS.

The WHO hazard classification of transfluthrin is “unlikely to present acute hazard in normal use.”

The draft specification and the supporting data were provided by Bayer AG, Leverkusen², in 2001.

Uses

Transfluthrin is a fast acting insecticide. It is used in household and hygiene products, mainly against flying insects, such as mosquitoes and flies, but also against material pests, such as moths (Pflanzenschutz Nachrichten Bayer, Special edition, 1995, Bayer AG, Leverkusen).

Identity

Common name

transfluthrin: E-ISO (published)

Synonyms

benfluthrin (Bayer), NAK 4455³

Chemical names

IUPAC: 2,3,5,6-tetrafluorobenzyl (1*R*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

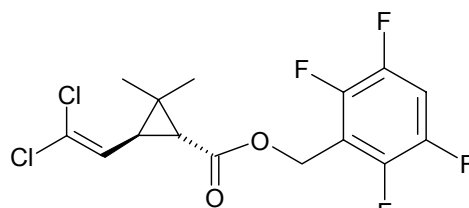
CA: (1*R-trans*)-(2,3,5,6-tetrafluorophenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate

¹ 2006 footnote: minor editorial corrections were introduced in 2006, mainly to clarify the CIPAC status of the analytical method for determination of transfluthrin.

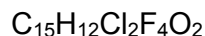
² 2006 footnote: the manufacturer informed WHO that, in 2002, all Bayer AG assets related to crop protection and environmental science business, including the supporting data, were transferred to Bayer CropScience, which currently has the ownership.

³ The development code, NAK 4455, is included because it appears in various references provided by the proposer.

Structural formula



Molecular formula



Relative molecular mass

371.2

CAS Registry number

118712-89-3

CIPAC code number

741

Identity tests

(GC retention time and IR spectrum (CIPAC Handbook K, p. 121, 2003); Enantioselective GC (CIPAC Handbook L, p. 128, 2006))

Physico-chemical properties

Table 1. Physico-chemical properties of pure transfluthrin

Parameter	Value(s) and conditions	Purity %	Method
Vapour pressure	9×10^{-4} Pa at 20°C	97.8	OECD 104
Melting point, boiling point and/or temperature of decomposition	melting point: 32°C boiling point: 242°C decomposition temperature: sublimes at $\geq 204^\circ\text{C}$	98	differential scanning calorimetry, OECD 103
Solubility in water	0.057 mg/l at 20°C	97.8	OECD 105
Octanol/water partition coefficient	$\log K_{OW} = 5.46$ at 20°C	97.8	OECD 107
Hydrolysis characteristics	half-life = >1 year at 25°C at pH 5 and pH 7 half-life = 14 days at 25°C at pH 9	min. 94	according to EPA Guideline, Subdivision N, § 161-1 (1982)
Photolysis characteristics	hardly affected by direct photo-degradation but accessible to natural photochemical degradation, through radical-induced oxidation	97.8	not stated
Dissociation characteristics	does not show basic or acidic properties in water	98.4	OECD 112, titration method

Table 2. Chemical composition and properties of transfluthrin technical material (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by WHO. Mass balances were 99.2 to 99.8%.
Declared minimum [a.i.] content	950 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	none
Relevant impurities < 1 g/kg and maximum limits for them:	none
Stabilisers or other additives and maximum limits for them:	none
Melting or boiling temperature range	32°C melting point, 242°C boiling point

Toxicological summaries

Notes.

- (i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from transfluthrin having impurity profiles to those referred to in the table above.
- (ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.
- (iii) A summary and references were provided by the proposer. Original reports were not submitted.
- (iv) The UK evaluation of transfluthrin (ACP 1997) was considered as part of this evaluation.

Table 3. Toxicology profile of transfluthrin technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Rat m/f	Oral	Acute, OECD 401	LD ₅₀ > 5000 mg/kg bw	17160
Mouse m/f	Oral	Acute, OECD 401	LD ₅₀ = 583-688 mg/kg bw	17156
Rat m/f	Dermal	Acute, OECD 402	LD ₅₀ >5000 mg/kg bw	17155
Mouse m/f	Dermal	Acute, OECD 402	LD ₅₀ \geq 4000 mg/kg bw	28471
Rat m/f	Inhalation	Acute, OECD 403	LC ₅₀ >513 mg/m ³	17216
Rabbit	Skin irritation	4 hours, occlusive, OECD 404	Not irritating	15804
Rabbit	Eye irritation	24 hours, OECD 405	Not irritating	15804
Guinea pig	Skin sensitization	Semi-occlusive, OECD 406 (Buehler Test)	Not sensitizing	17920
Guinea pig	Skin sensitization	Semi-occlusive, OECD 406 (M&K)	Not sensitizing	17964

Transfluthrin is of low acute toxicity in the rat, with an LD₅₀ of >5000 mg/kg bw via each route of administration and with an acute and dermal NOEL of 100 mg/kg bw/d. The 4 h LC₅₀ was >513 mg/m³ air for male and female rats. The only sign noted during the 14 d observation period was a slight tremor in females for 5 minutes after dosing. Transfluthrin is not a skin or eye irritant, nor a skin sensitizer.

Table 4. Toxicology profile of transfluthrin technical material based on repeated administration (sub-acute to chronic).

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Rat m/f	Sub-acute oral	Sub-acute, 28 days, OECD 407 0-10-50-250 mg/kg	NOEL = 50 mg/kg bw/d	19187
Rabbit m/f	Sub-acute dermal	Sub-acute, 15 days, OECD 410 0-20-200-2000 mg/kg	NOEL = 1000 mg/kg bw/d	19236
Rat m/f	Sub-acute inhalation	Sub-acute, 4 weeks, OECD 412 0-1.6-6.6-36.6-168.1 mg/m ³ air (6 h/d; 5 d/wk)	NOEL = 36.6 mg/m ³ (≅ 13 mg/kg bw/d)	17588
Dog m/f	Sub-chronic oral diet	Sub-chronic, 13 weeks, OECD 409 0-50-350-2500 ppm	NOEL = 50 ppm (≅ 1.9 mg/kg bw/d)	R4723
Rat m/f	Sub-chronic oral diet	Sub-chronic, 13-18 weeks 0-10-50-500-5000 ppm	NOEL = 50 ppm (≅ 3.5 mg/kg bw/d)	19756
Rat m/f	Sub-chronic inhalation	Sub-chronic, 90 days 0-4.9-46.7-220.2 mg/m ³ air (6 h/d; 5 d/wk)	LOEL = 46.7 mg/m ³ (≅ 17 mg/kg bw/d)	18417
Dog m/f	Chronic oral diet	Chronic, 52 weeks, OECD 452 0-30-300-3,000 ppm	NOEL < 30ppm (≅ 0.75 mg/kg bw/d)	22638
Dog m/f	Chronic oral diet	Chronic, 53 weeks, OECD 452. 0-10 ppm	NOEL = 10ppm (≅ 0.25 mg/kg bw/d)	22678
Rat m/f	Carcinogenicity and Chronic toxicity diet	Chronic, 2 years, OECD 453 0-20-200-2,000 ppm	NOEL = 20 ppm (≅ 1,0 mg/kg) NOEL for carcinogenicity = 200 ppm (≅ 9.9 mg/kg bw/d)	22375
Mouse m/f	Carcinogenicity and chronic toxicity diet	Oral feed, 2 years, OECD 451. 10, 100, and 1000 ppm diet, i.e. 2, 20, and 200 mg/kg bw/d for males, 3, 33 and 280 mg/kg bw/d for females	Males: NOAEL = 100 ppm (≅ 20mg/kg bw/d) Females: NOEL could not be determined as clinical changes were observed at the lowest dose level. Liver adenomas were observed in females at 1000 ppm dose level	22744
Rat m/f	Multi-generation study oral diet	Oral diet, 84 days, OECD 416 0-20-200-1000ppm	NOAEL = 220ppm Parental NOAEL = 200ppm (= 9 to 38 mg/kg) Neonatal NOAEL = 1,000ppm (= 50 mg/kg calculated) Reproductive NOAEL = 1,000 ppm (= 45 to 191 mg/kg)	R5352
Rat f	Developmental toxicity, gavage	10 days 0-25-55-125 mg/kg/d	Maternal NOAEL = 25mg/kg bw/d Developmental NOAEL = 125mg/kg bw/d	MTD0058
Rabbit f	Developmental toxicity, oral feed [gavage]	13 days 0-15-50-150 mg/kg/d	Maternal NOAEL = 15mg/kg bw/d Developmental NOAEL = 150 mg/kg bw/d	18069

In the rat, mortalities and body tremors were seen at 250 mg/kg/d following gavage dosing. There were no mortalities following dietary administration of up 5000 ppm (approximately 40 mg/kg bw/d).

A low incidence of urinary bladder papillomas/carcinomas was observed in rats at a dietary level of 2000 ppm of transfluthrin¹. In female mice, an increased incidence of liver adenomas, but not of carcinomas, was observed at 1000 ppm, the highest dose level tested. In 2-stage studies on promoting effects in rat liver cells with diethylnitrosamine as the initiator, transfluthrin had no initiating activity but was a weak promotor (22888). Transfluthrin did not induce hepatocyte proliferation or increase mitoses in the liver *in vivo* (R5555).

Developmental studies in both the rat and rabbit provided no evidence of teratogenicity when transfluthrin was administered at doses up to 125 and 150 mg/kg bw/d, respectively. NOELs of 25 and 15 mg/kg bw/d were established for maternal toxicity in the rat and rabbit respectively.

In a dietary multi-generation reproductive toxicity study in the rat, there was no evidence of teratogenicity, foetotoxicity or reproductive toxicity in rats administered transfluthrin at doses up to 191 mg/kg bw/d. NOELs of 45 to 191 and 9 to 38 mg/kg bw/d were established for reproductive and parental toxicity, respectively.

Table 5. Mutagenicity profile of the transfluthrin technical material based on *in vitro* and *in vivo* tests.

Test system	Test object	Concentration	Purity	Results	Reference
<i>In vitro, Point mutation assays</i>					
Salmonella microsome test	<i>S. typhimurium</i> (TA 98, TA 100, TA 1535, TA 1537)	20 to 12500 µg/plate, with and without S9 activation	96.0%	negative	15144
Salmonella microsome test	<i>S. typhimurium</i> (TA 98, TA 100, TA 1535, TA 1537)	20 to 12500 µg/plate, with and without S9 activation	94.5%	negative	16084
HPRT-test	Chinese hamster ovary (CHO) cells	25 to 100 µg/ml, with and without S9 activation	94.8%	negative	18148
mitotic recombination assay	<i>Saccharomyces cerevisiae</i> D7	625 to 10000 µg/ml, with and without S9 activation	94.5%	negative	16083
<i>In vitro, DNA damage assays</i>					
unscheduled DNA synthesis	primary rat hepatocytes	1 to 500 µg/ml	94.9%	negative	21313
sister chromatid exchange	Chinese hamster ovary (CHO) cells	0.0667 to 2000 µg/ml with and without S9 activation	94.8%	negative	R4718
<i>In vivo, DNA damage assays</i>					
unscheduled DNA synthesis	mouse BOR:CFW1 hepatocytes	780 and 5580 mg/kg body weight	95.0%	negative	R3658
<i>In vitro, Chromosomal damage/aberration assays</i>					
cytogenetic study	human lymphocytes	50 to 200 µg/ml, with and without S9 activation	94.8%, 95.0%	negative	18742
<i>In vivo, Chromosomal damage/aberration assays</i>					

¹ The proposer noted that the effect was most likely attributable to a non-genotoxic mechanism of chronic urothelial irritation and regeneration, induced by transfluthrin or one of its metabolites (Cohen & Ellwein 1990; Bayer 1999).

Test system	Test object	Concentration	Purity	Results	Reference
micronucleus test	male and female NMRI-mouse bone marrow cells	375 mg/kg body weight	95.0%	negative	16912
³² P-post-labelling assay for detection of adduct formation	male and female Wistar-rat hepatocytes and urinary bladder cells	7 x 100 and 7 x 250 mg/kg body weight	94.7%	negative	R6335

Transfluthrin was not mutagenic *in vitro* in bacteria, yeast or mammalian cells with or without metabolic activation, neither was there any evidence of mutagenicity from *in vivo* tests on rats and mice.

Table 6. Ecotoxicology profile of transfluthrin technical material.

Species	Test	Duration and conditions	Result	Reference
<i>Colinus virginianus</i> (bobwhite quail)	Acute toxicity	14 days, OECD 401	LD ₅₀ > 2000 mg/kg NOEL = 2000 mg/kg	VB-003
<i>Serinus canarius</i> (Canary bird)	Acute toxicity	14 days, OECD 401	LD ₅₀ > 2000 mg/kg NOEL = 2000 mg/kg	VK315
<i>Salmo gairdneri</i> (rainbow trout)	Acute (flow through conditions)	96 hours, OECD 203	LC ₅₀ = 0.7 µg/l NOEC = 0.5 µg/l *	FF-220
<i>Leuciscus idus melanotus</i> (golden orfe)	Acute (flow through conditions)	96 hours, OECD 203	LC ₅₀ = 1.25 µg/l NOEC = 0.89 µg/l	F0-1108
<i>Daphnia magna</i> (water flea)	Acute toxicity	48 hours, OECD 202	EC ₅₀ = 1.2 µg/l NOEC = 0.33 µg/l	1091 A/01 D
<i>Scenedesmus subspicatus</i> (green alga)	Growth inhibition	72 hours, OECD 201	EC ₅₀ > 0.044mg/l NOEC = 0.017 mg/l	1091 A/01 AI
<i>Eisenia foetida</i> (earthworm)	Acute toxicity	14 days, OECD 207	LC ₅₀ = 194 mg/kg NOEC = 32 mg/kg	HBF/RG15 2
Activated sludge	Microbial respiration rate inhibition	3 hours, OECD 209	EC ₅₀ = 10 000 mg/l	1091 A/01 B

* It was unclear why the difference between LC₅₀ and NOEC values was so small.

Environmental fate and behaviour

Tests of hydrolysis for transfluthrin at 25°C for 36 d gave a half-life of 14 d at pH 9 and >1 year at pH 7 and 5. Under the test conditions transfluthrin did not readily hydrolyse and, considering the very low water solubility and strong adsorption characteristics of the compound, hydrolysis is expected to play a minor role in the degradation of transfluthrin in the environment.

Transfluthrin underwent photolysis when irradiated with light of wavelengths > 290 nm with an extrapolated half-life of 17 h¹. A calculation to determine the rate of degradation of transfluthrin in air estimated the half-life to be 4.1 d.

¹ The UV absorption spectrum of transfluthrin indicates that direct photodegradation should not occur. Indirect photodegradation, by radicals generated coincidentally in the surrounding medium, was responsible for an extrapolated half-life of 17 h. In a more recent study, the half-life of indirect photodegradation was determined as 26 h (3467).

Hazard summary

Environmental toxicity tests showed that transfluthrin is of low toxicity to algae, earthworms and birds but is highly toxic to fish and daphnia. If classified using the criteria laid out in the Globally Harmonized System for classification and labelling of chemicals (UN, 2003), transfluthrin would be classified in the category Acute I, in its lower band.

Transfluthrin has not been evaluated by the WHO IPCS but the IPCS hazard classification based on acute toxicity of transfluthrin is "*unlikely to present acute hazard in normal use*" (WHO, 2002).

The FAO/WHO JMPR has not evaluated transfluthrin but the UK evaluation of the compound (ACP, 1997) was considered as part of this evaluation. The Australian Therapeutic Goods Administration of the Commonwealth Department of Health and Ageing has set an ADI of 0 to 0.003 mg/kg/d, based on the NOEL of 0.25 mg/kg bw/d for chronic dietary intake by dogs (TGA 2001).

Formulations

The main formulation types available are mosquito coils (MC) and liquid vaporizers (LV), which are registered and sold in many countries throughout the world.

Methods of analysis and testing

The analytical methods for determination of transfluthrin (including identity tests) in the TC, SL and LV are full CIPAC methods (CIPAC 2003, CIPAC 2006). Transfluthrin is determined by capillary gas chromatography with internal standardization (dipentylphthalate) and flame ionization detection.

Test methods for determination of the physical-chemical properties of technical active ingredient were mainly OECD.

Physical properties

The limits proposed for physical properties (acidity and alkalinity) of the technical material and the methods for testing them comply with the requirements of the FAO/WHO Manual (FAO/WHO, 2002).

Containers and packaging

The technical active may be stored in glass containers, plastic containers or steel drums with appropriate plastic bags.

Expression of the active ingredient

The active ingredient content is expressed as transfluthrin in g/kg.

Appraisal

There is currently no WHO specification for transfluthrin and this was a new application by Bayer AG, Leverkusen.

Transfluthrin is a synthetic pyrethroid insecticide used in household and hygiene products, mainly for the control of flying insects such as mosquitoes and flies. It has been approved for use in about 50 countries worldwide. The main formulation types

available are mosquito coils and aerosols. Evaluation of specifications for public health use was restricted to the TC.

Transfluthrin is of low acute and dermal toxicity and is classified as unlikely to present acute toxicity in normal use by the IPCS. It is not a skin or eye irritant, nor a skin sensitizer.

In a dietary multi-generation reproductive toxicity study in the rat, there was no evidence of teratogenicity, foetotoxicity or reproductive toxicity in rats administered transfluthrin at doses up to 191 mg/kg bw/d.

Transfluthrin induced a low frequency of urinary bladder adenomas/carcinomas in rats at high doses – the NOEL for non-cancer endpoints was 20 ppm, for cancer, 200 ppm, and the urinary tumours were observed at a level of 2000 ppm diet. It also induced adenomas in female mice at a high dose level. Transfluthrin had no initiating activity, but was a weak promotor of carcinogenicity. Transfluthrin was consistently negative in mutagenicity studies *in vitro* and *in vivo*; it is concluded that the tumours induced at high dose in rats and female mice are probably not produced by a genotoxic mechanism. Field and laboratory tests showed that transfluthrin is of low toxicity to algae, birds and earthworms but it is highly toxic to fish and aquatic invertebrates such as daphnia.

If classified according to the Globally Harmonized System for classification and labelling of chemicals, transfluthrin would be classified in category Acute I, lower band.

The FAO/WHO JMPR has not evaluated transfluthrin. However, the Australian authorities have set an ADI of 0 to 0.003 mg/kg bw/d (TGA 2001).

The meeting considered the issue of relevant impurities. WHO/PCS noted that the toxicity studies were all performed using transfluthrin with "similar" impurity profiles and the results showed not only a generally low toxicity but also the absence of unexpected effects. Information provided by the proposer indicated that, at the levels found in the 5 batch analysis, none of the impurities is likely to be associated with important toxic effects. WHO/PCS therefore concluded that none of the impurities was relevant and the meeting concurred with this view.

There were some minor differences in the declared composition of the technical material submitted for registration in the UK and that submitted to the WHO, in that the batch analysis data and manufacturing limits submitted to WHO indicated somewhat lower concentrations of certain impurities. The proposer explained that these were due to improvements in the quality of raw materials used and manufacturing improvements, made as part of the transition from pilot-scale to large-scale production.

CIPAC has adopted the analytical method for determination of the active ingredient in the technical material (including identity tests based on diastereoisomer ratio and stereoisomer ratios and infra-red spectroscopy) and in SL and LV formulations, which renders it acceptable for support of the specification for the TC. Transfluthrin is determined by capillary gas chromatography with internal standardization. The proposer has verified that the analytical method is capable of separation of the diastereoisomers of transfluthrin, i.e. that the corresponding *cis*-isomers would be separated and detected if present and would not be included in the measurement of transfluthrin (CIPAC, 2003).

Recommendations

The meeting recommended that the proposed specification for the technical material should be adopted by WHO¹.

References

Bayer document number or other reference	Year and title of report or publication details
1091 A/01 AI	2001. NAK 4455 (Bayothrin) - Acute Daphnia toxicity.
1091 A/01 B	2001. NAK 4455 (Bayothrin) Toxicity to bacteria.
1091 A/01 D	2001. NAK 4455 (Bayothrin) - Acute Daphnia toxicity.
15144	1986. NAK 4455, <i>Salmonella</i> microsome test to evaluate for point-mutagenic effect.
15804	1987. NAK 4455, study for irritant/corrosive potential for skin and eye (rabbit).
16083	1987. NAK 4455, test on <i>S. cerevisiae</i> D7 for the induction of mitotic recombination.
16084	1987. NAK 4455 techn., <i>Salmonella</i> microsome test to evaluate for point-mutagenic effect.
16912	1988. NAK 4455, micronucleus test on the mouse to evaluate for clastogenic effects.
17155	1988. NAK 4455 techn., study for acute dermal toxicity to rats.
17156	1988. NAK 4455 techn., study for acute oral toxicity to mice.
17160	1988. NAK 4455 techn., study for acute oral toxicity to rats.
17216	1988. NAK 4455 (c.n.: Benfluthrin, proposed), study for subacute inhalation toxicity to OECD guideline no. 403.
17588	1989. NAK 4455 (c.n.: Benfluthrin, suggested), study for subacute inhalation toxicity to the rat to OECD guideline no. 412.
17920	1989. NAK 4455 techn., study for skin-sensitizing effect on guinea pigs (Buehler test).
17964	1989. NAK 4455 techn., studies for skin-sensitizing effect on guinea-pig (Magnusson and Kligman's Maximization test).
18069	1989. NAK 4455, study for embryotoxic effects on rabbits after oral administration.
18148	1989. NAK 4455, mutagenicity study for the detection of induced forward mutations in the CHO-HGPRT assay <i>in vitro</i> .
18417	1989. NAK 4455 (c.n.: Benfluthrin, suggested), study for subchronic inhalation toxicity to the rat.
18742	1990. NAK 4455, <i>in vitro</i> cytogenetic study with human lymphocytes for the detection of induced clastogenic effects.
19187	1990. NAK 4455, subacute oral study of toxicity to rats.
19236	1990. NAK 4455 techn., subacute dermal study of toxicity to rabbits.
19756	1990. Subchronic toxicological study in rats (administration in the diet for up to 18 weeks).
21313	1992. NAK 4455, mutagenicity test on unscheduled DNA synthesis in rat liver primary cell cultures <i>in vitro</i> .
22375	1993. NAK 4455, study for chronic toxicity and cancerogenicity in Wistar rats (administration in the diet for 2 years).
22638	1993. NAK 4455, chronic toxicity study in dogs (52-week feeding study).
22678	1993. NAK 4455, chronic toxicity study in dogs with oral administration (52-week feeding study).

¹ In 2004, following submissions of additional information and stating that new 5-batch analytical data would be generated to support production of the TC at a new site, the manufacturer requested reconsideration of the data and specification by the JMPS. Therefore the specification recommended for adoption in 2002 was not published.

Bayer document number or other reference	Year and title of report or publication details
22744	1993. NAK 4455, study for oncogenicity in B6C3F1 mice after administration in the diet for two years.
22888	1994. NAK 4455, study for possible promotion effect of the liver of male Wistar rats (Administration in diet for approx. 8 weeks).
28471	1999. NAK 4455 (c.n. Transfluthrin (prop.)) – study for acute dermal toxicity in mice.
3467	1991. Experiments concerning the indirect photodegradation of Benfluthrin in aqueous solutions.
ACP 1997	Transfluthrin Use as a Public Hygiene Insecticide – An Evaluation by the Advisory Committee on Pesticides, United Kingdom, September 1997.
Bayer 1999	1999. Transfluthrin evaluation bioassay of carcinogenicity. Expert Opinion.
CIPAC, 2003	Transfluthrin Technical and Transfluthrin SL, CIPAC Handbook K, p. 121
CIPAC, 2006	Transfluthrin Technical, Stereospecific Identity Test and Transfluthrin LV, CIPAC Handbook L, p. 128
Cohen & Ellwein, 1990	S. M. Cohen and L.B. Ellwein. Cell proliferation in carcinogenesis. <i>Science</i> 249 , 1007-1011, 1990.
F0-1108	1988. Acute toxicity of NAK 4455 to golden orf (<i>Leuciscus idus melanotus</i>) in a flow-through-test.
FAO 1999	Manual on Development and Use of FAO and WHO Specifications for Pesticides, 1 st Edition, Rome 2002.
FF-220	1988. Acute toxicity of NAK 4455 to rainbow trout (<i>Salmo Gairdneri</i>) in a flow-through-test.
HBF/RG152	1991. Toxicity of NAK 4455 (techn.) to earthworms.
MTD0058	1988. Teratology study in the rat with NAK 4455.
R3658	1986. Influence of NAK 4455 on DNA metabolism.
R4718	1989. Mutagenicity test on NAK 4455 in an in vitro cytogenicity assay measuring sister chromatid exchange frequencies in Chinese hamster ovary (CHO) cells.
R4723	1989. 13-week oral toxicity (feeding) study with NAK 4455 tech. in the dog.
R5352	1991. NAK 4455 technical, multiple generation reproduction study in rats.
R5555	1992. Cell proliferation study in rats treated with NAK 4455.
R6335	1995. ³² P post-labelling assay for detection of adduct formation by transfluthrin (NAK 4455) in rat liver and urinary bladder DNA.
TGA 2001	ADI List, Therapeutic Goods Administration, Commonwealth Department of Health and Ageing, Australia. December 2001.
UN 2003	Globally Harmonized System of Classification and Labelling of Chemicals. United Nations, New York and Geneva, 2003.
VB-003	1987. Acute oral LD50 of NAK 4455 to bobwhite quail.
VK315	1987. Acute oral LD50 of NAK 4455 to the canary bird (<i>Serinus canarius</i>).
WHO, 2002	The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2000-2002, Document WHO/PCS/01.5. WHO, Geneva, 2002.